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Published in:
Clinical and Experimental Allergy

DOI:
10.1111/cea.13057

Publication date:
2017

Document Version
Peer reviewed version

CLINICAL & EXPERIMENTAL ALLERGY

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Journal:	*Clinical and Experimental Allergy*
Manuscript ID	CEA-2017-0282.R1
Manuscript Type:	Research Letter
Date Submitted by the Author:	18-Oct-2017
Complete List of Authors:	Jabbal, Sunny; University of Dundee School of Medicine, Scottish Centre for Respiratory Research Lipworth, Brian; University of Dundee, Asthma & Allergy Research Group
Keywords:	asthma, eosinophils, pneumology
Additional Keywords:	nitric oxide

Blood eosinophils: The forgotten man of inhaled steroid dose titration

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Declaration of funding: Existing departmental funds

Trial registration: Not applicable

Conflicts of Interest: BJL has received payment for giving talks from Teva ,Meda and Chiesi and Boerhinger Ingelheim , for consulting activity from Chiesi ,Cipla ,Dr Reggys ,Lupin and Sandoz ,for attending meetings from Teva and Boerhinger Ingelheim , for unrestricted research grants from Teva and Chiesi and Meda and multicentre grants from Chiesi , Astrazeneca ,Sanofi , Janssen and Teva. SJ has received reimbursement for attending symposia from Astra Zeneca, Chiesi Limited, NAPP, and Teva Pharmaceuticals. SJ has received fees for speaking from Chiesi Limited, NAPP, Boehringer Ingelheim, Pfizer and Astra Zeneca.

Word Count: 1012

Figures: 1

Tables: 1

Abbreviations:

BPD	beclometasone equivalent dose
ECP	eosinophilic cationic protein
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
IL-5	Interleukin-5
ICS	Inhaled corticosteroid
LTRA	Leukotriene receptor antagonist

Blood eosinophil counts which were once regarded as normal, have become of increasing interest in the era of Interluekin-5 (IL-5) asthma treatment. Blood eosinophils as low as 150 cells/μL have been suggested as treatment cut-offs for eosinophil depleting therapies such as mepolizumab [1], whilst a value of 300 cells/μL has been deemed a more pragmatic cut off by the National Institute for Health and Care Excellence (United Kingdom). In this era of eosinophil post-truths, inhaled corticosteroids (ICS), the eosinophil's oldest adversary, are very much the forgotten man.

Corticosteroids reduce the numbers of eosinophils in blood and sputum by inhibiting the expression of pro eosinophilic cytokines such as IL-5, and increase the rate of apoptosis and associated phagocytosis. It is known that titrating ICS against sputum eosinophils results in improved asthma control[2]. Whilst it is also known that sputum eosinophils correlate well with blood eosinophils [3], the effects of increasing ICS dose on blood eosinophils are less well documented [4].

We therefore wanted to know if ICS dose titration suppresses blood eosinophil counts in patients with persistent asthma. In addition, we investigated whether leukotriene receptor antagonists (LTRA) has a similar effect when used as add on therapy. Another surrogate marker of TH2 mediated inflammation is exhaled breath nitric oxide (FeNO), where it has already been demonstrated that there is a dose-response effect of ICS[5].

We, therefore, performed a pooled analysis of our own studies performed by the Scottish Centre for Respiratory Research, where we measured blood eosinophils and FeNO from a baseline of none or low dose ICS to medium dose ICS with or without LTRA. Fourteen studies were included in this analysis, and are listed in table 1. All were approved by the East of Scotland Regional Ethics Committee and registered at clinicaltrials.gov.

217 non-smoking patients with mild-moderate persistent asthma patients were included in the ICS dose titration analysis, of these 144 also received additive LTRA. Patients had a mean age of 38 years, and a mean FEV1 of 85% predicted. In all studies analysed patients must have been free from an asthma exacerbation requiring systemic corticosteroids in the three months prior to trial enrolment. In the nine out of fourteen studies included, patients had at least one positive skin prick test to a common aeroallergen, with a mean number of positive tests of two.

Baseline median low dose inhaled corticosteroid (ICS) dose was 200µg/day as beclometasone diproprionate (BDP) equivalent dose .Baseline mean eosinophils were 356 cells/µL, mean eosinophilic cationic protein (ECP) was 24.9 µg/L, and mean exhaled nitric oxide (FeNO) was 41.4 ppb. Participants were stepped up to medium dose ICS as median 800 µg/day BDP equivalent, with a median treatment duration of two weeks. Median treatment duration of additive LTRA was also two weeks.

Changes in blood eosinophils and FeNO are presented in figure 1. We observed a significant mean fall in eosinophils of 71 cells/µL (95% CI 38 to 105) p=0.001 comparing low versus medium dose ICS, and a further non-significant fall with LTRA amounting to 20 cells/µL. FeNO also significantly fell by 14.5ppb (95% CI 7.9 to 21.1), p=0.001 comparing low and medium dose ICS, but did not decrease further with addition of LTRA. Mean ECP levels for low and medium dose ICS were 24.9 µg/L and 18.8 µg/L respectively, representing a significant (p=0.005) decrease of 6.1 µg/L (95% CI 2.4 to 9.6), although, there were insufficient data to assess effects of LTRA. FEV_1% predicted did not significantly change between low and medium dose ICS: 1.6% (95% CI -0.5 to 3.2).

We demonstrated that ICS even at a medium dose of 800ug BDP results in a significant fall in blood eosinophils over a period of two weeks. Our data showed a non-significant further fall in

blood eosinophils amounting to 20 cells/μL when adding LTRA, while Laviolette et al found a significant additive effect of LTRA amounting to a mean change of 40 cells [6]. In contrast Greene et al found no significant additive fall with LTRA on top of ICS , albeit measuring sputum rather than blood eosinophils[7]. Their study also found no significant additive effect on FeNO in keeping with our data. In terms of ICS dose response, Kips et al reported significantly lower sputum eosinophils comparing medium and low dose ICS, but no commensurate fall in sputum ECP [8] , in contrast to our observation of a significant fall in both blood eosinophils and ECP.

In a retrospective observational cohort study, Price et al. demonstrated that those with eosinophils ≥400 cells/μL experience more severe exacerbations and have worse asthma control [9]. The fundamental question therefore is whether ICS dose should be titrated against blood eosinophils as a surrogate inflammatory marker, especially given that pulmonary function shows a plateau in response above 400ug/day BDP equivalent dose [10]. In this regard Green et al showed that titrating ICS against sputum eosinophils resulted in significantly reduced exacerbations [2]; whether the same outcome would be achieved by titrating against blood remains to be answered. We appreciate the limitations of our data which were only short term and we did not report any outcomes of asthma control. Furthermore, the observed effect might be due to possible systemic absorption from the lung, assessment of which would have required a surrogate marker of systemic cortisol suppression. Finally, our study lacks a placebo arm or a control arm with a fixed ICS dose, meaning we are unable to account for natural variation in blood eosinophils over time. In a more sever cohort of asthma patients, it has been demonstrated for subjects who have an initial blood eosinophil count above 150 cells/μl, 85% of them remain

above this value, even up to 56 weeks (based on four weekly blood eosinophil measurements) [11].

As we consider ever more complex anti-inflammatory therapies as the future of asthma care, we must not overlook inhaled corticosteroids and their effects on blood eosinophils as the forgotten man of asthma therapy. Perhaps a randomized control trial comparing ICS dose titration against conventional markers (pulmonary function, reliever use, and symptoms) versus titration against blood eosinophils over one year might be worth pursuing.

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Figure legend

Comparison of low (200ug BDP equivalent) and medium dose (800ug BDP equivalent) inhaled corticosteroid (ICS) on blood eosinophils (top) and exhaled breath nitric oxide (bottom) in n=217 asthma patients, depicted as means and SEM. Effects of add on therapy with leukotriene receptor antagonists (LTRA) are also shown in 144 patients.

Table 1. Source data

Reference	ICS dose (BDP µg equivalent)	Total Exposure (days)
1. Lipworth BJ et al. Am J Med 2000; 109:114-21.	600µg +/- LTRA	14
2. Aziz I et al. Chest 2000; 118:1049-58.	400-800ug	28
3. Wilson AM et al Chest 2001; 119:1021-6.	800µg +/-LTRA	14
4. Dempsey OJ et al. J Allergy Clin Immunol 2002; 109:68-74.	0-400µg	28
5. Currie GP et al. Am J Respir Crit Care Med 2003; 167:1232-8.	500µg-1000µg	21
6. Currie GP et al. Allergy 2003; 58:602-7.	0-400µg	14
7. Sims EJ et al. Br J Clin Pharmacol 2003; 56:104-11.	500µg +/-LTRA	14
8. Anderson WJ et al. Clin Sci (Lond) 2014; 127:635-43.	200 -800µg	42
9. Anderson WJ et al. Chest 2012; 142:1553-61.	200-1000µg	28
10. Lipworth BJ et al. Chest 2012; 141:607-15.	400-1200µg	365
11. Menzies D et al. Allergy 2007; 62:661-7.	200-800µg+/- LTRA	35
12. Barnes ML et al. Allergy 2007; 62:73-80.	0-400µg	70
13. Dempsey OJ et al. Chest 2002; 122:151-9.	100-400µg +/- LTRA	42
14. Wilson AM et al. Br J Clin Pharmacol 1999; 48:579-85.	1000-2000µg	8

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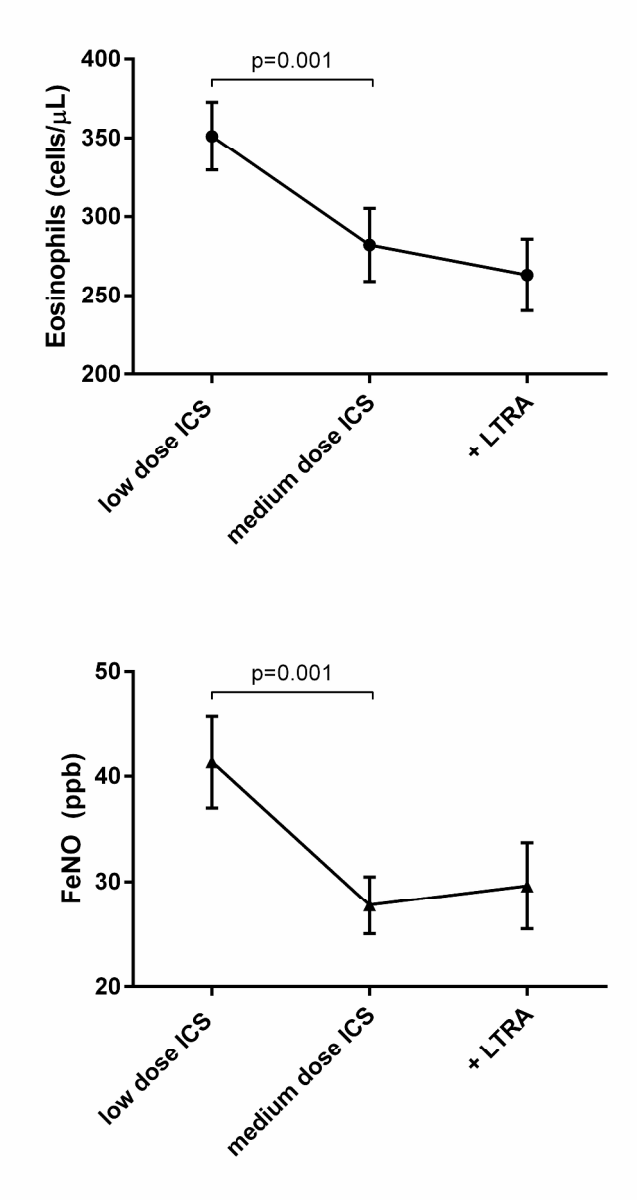

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266x502mm (300 x 300 DPI)